SUMMARY: The Food and Drug Administration (FDA) is announcing that Eastman Chemical Co. has filed a petition proposing that the food additive regulations be amended to provide for the safe use of 1,4-cyclohexanedimethanol as a polyhydric alcohol for use in polyester resins intended for coatings in contact with food.

DATES: Written comments on the petitioner's environmental assessment by August 11, 1997.

ADDRESSES: Submit written comments to the Dockets Management Branch (HFA-305), Food and Drug Administration, 12420 Parklawn Dr., rm. 1-23, Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT: Hortense S. Macon, Center for Food Safety and Applied Nutrition (HFS-205), Food and Drug Administration, 200 C St. SW., Washington, DC 20204, 202-418-3086.

SUPPLEMENTARY INFORMATION: Under the Federal Food, Drug, and Cosmetic Act (sec. 409(b)(5) (21 U.S.C. 348(b)(5))), notice is given that a food additive petition (FAP 7B4547) has been filed by the Eastman Chemical Co., P.O. Box 1994, Kingsport, TN 37662. The petition proposes to amend the food additive regulations in § 175.300 *Resinous and polymeric coatings* (21 CFR 175.300) to provide for the safe use of 1,4-cyclohexanedimethanol as a polyhydric alcohol for use in polyester resins intended for coatings in contact with food.

The potential environmental impact of this action is being reviewed. To encourage public participation consistent with regulations promulgated under the National Environmental Policy Act (40 CFR 1501.4(b)), the agency is placing the environmental assessment submitted with the petition that is the subject of this notice on public display at the Dockets Management Branch (address above) for public review and comment. Interested persons may, on or before August 11, 1997, submit to the Dockets Management Branch (address above) written comments. Two copies of any comments are to be submitted, except that individuals may submit one copy. Comments are to be identified with the docket number found in brackets in the heading of this document. Received comments may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday. FDA will also place on public display any amendments to, or comments on, the petitioner's environmental assessment without further announcement in the **Federal Register**. If, based on its review, the agency finds that an environmental impact statement is not required and this petition results in a regulation, the notice of availability of the agency's finding of no significant impact and the evidence supporting that finding will be published with the regulation in the **Federal Register** in accordance with 21 CFR 25.40(c).

Dated: June 24, 1997.

Laura M. Tarantino,

Acting Director, Office of Premarket Approval, Center for Food Safety and Applied Nutrition.

[FR Doc. 97-18127 Filed 7-10-97; 8:45 am]

BILLING CODE 4160-01-F

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. 96E-0386]

Determination of Regulatory Review Period for Purposes of Patent Extension; ALLEGRA™

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) has determined the regulatory review period for ALLEGRA™ and is publishing this notice of that determination as required by law. FDA has made the determination because of the submission of an application to the Commissioner of Patents and Trademarks, Department of Commerce, for the extension of a patent which claims that human drug product.

ADDRESSES: Written comments and petitions should be directed to the Dockets Management Branch (HFA-305), Food and Drug Administration, 12420 Parklawn Dr., rm. 1-23, Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT: Brian J. Malkin, Office of Health Affairs (HFY-20), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-443-1382.

SUPPLEMENTARY INFORMATION: The Drug Price Competition and Patent Term Restoration Act of 1984 (Pub. L. 98-417) and the Generic Animal Drug and Patent Term Restoration Act (Pub. L. 100-670) generally provide that a patent may be extended for a period of up to 5 years so long as the patented item (human drug product, animal drug product, medical device, food additive, or color additive) was subject to regulatory review by FDA before the item was marketed. Under these acts, a product's regulatory review period forms the basis for determining the amount of extension an applicant may receive.

A regulatory review period consists of two periods of time: A testing phase and an approval phase. For human drug products, the testing phase begins when the exemption to permit the clinical investigations of the drug becomes effective and runs until the approval phase begins. The approval phase starts with the initial submission of an application to market the human drug product and continues until FDA grants permission to market the drug product. Although only a portion of a regulatory review period may count toward the actual amount of extension that the Commissioner of Patents and Trademarks may award (for example, half the testing phase must be subtracted as well as any time that may have occurred before the patent was issued), FDA's determination of the length of a regulatory review period for a human drug product will include all of the testing phase and approval phase as specified in 35 U.S.C. 156(g)(1)(B).

FDA recently approved for marketing the human drug product ALLEGRA™ (fexofenadine hydrochloride). ALLEGRA™ is indicated for the relief of symptoms associated with seasonal allergic rhinitis in adults and children 12 years of age and older. Symptoms treated effectively include sneezing, rhinorrhea, itchy nose/palate/throat, itchy/watery/red eyes. Subsequent to this approval, the Patent and Trademark Office received a patent term restoration application for ALLEGRA™ (U.S. Patent No. 4,254,129) from Hoechst Marion Roussel, Inc., and the Patent and Trademark Office requested FDA's assistance in determining this patent's eligibility for patent term restoration. In a letter dated March 7, 1997, FDA advised the Patent and Trademark office that this human drug product had undergone a regulatory review period and that the approval of ALLEGRA™ represented the first permitted commercial marketing or use of the product. Shortly thereafter, the Patent and Trademark Office requested that FDA determine the product's regulatory review period.

FDA has determined that the applicable regulatory review period for ALLEGRA™ is 996 days. Of this time, 635 days occurred during the testing phase of the regulatory review period, while 361 days occurred during the approval phase. These periods of time were derived from the following dates:

1. *The date an exemption under section 505(i) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(i)) became effective*: November 4, 1993.

FDA has verified the applicant's claim that the date that the investigational new drug application became effective was on November 4, 1993.

2. *The date the application was initially submitted with respect to the human drug product under section 505(b) of the Federal Food, Drug, and Cosmetic Act*: July 31, 1995. FDA has verified the applicant's claim that the new drug application (NDA) for ALLEGRA™ (NDA 20-625) was initially submitted on July 31, 1995.

3. *The date the application was approved*: July 25, 1996. FDA has verified the applicant's claim that NDA 20-625 was approved on July 25, 1996.

This determination of the regulatory review period establishes the maximum potential length of a patent extension. However, the U.S. Patent and Trademark Office applies several statutory limitations in its calculations of the actual period for patent extension. In its application for patent extension, this applicant seeks 677 days of patent term extension.

Anyone with knowledge that any of the dates as published is incorrect may, on or before September 9, 1997, submit to the Dockets Management Branch (address above) written comments and ask for a redetermination. Furthermore, any interested person may petition FDA, on or before January 7, 1998, for a determination regarding whether the applicant for extension acted with due diligence during the regulatory review period. To meet its burden, the petition must contain sufficient facts to merit an FDA investigation. (See H. Rept. 857, part 1, 98th Cong., 2d sess., pp. 41-42, 1984.) Petitions should be in the format specified in 21 CFR 10.30.

Comments and petitions should be submitted to the Dockets Management Branch (address above) in three copies (except that individuals may submit single copies) and identified with the docket number found in brackets in the heading of this document. Comments and petitions may be seen in the Dockets Management Branch between 9 a.m. and 4 p.m., Monday through Friday.

Dated: June 30, 1997.

Allen B. Duncan,

Acting Associate Commissioner for Health Affairs.

[FR Doc. 97-18125 Filed 7-10-97; 8:45 am]

BILLING CODE 4160-01-F

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

Advisory Committee; Notice of Meeting

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

This notice announces a forthcoming meeting of a public advisory committee of the Food and Drug Administration (FDA). The meeting will be open to the public.

Name of Committee: Radiological Devices Panel of the Medical Devices Advisory Committee.

General Function of the Committee: To provide advice and recommendations to the agency on FDA regulatory issues.

Date and Time: The meeting will be held on August 18, 1997, 9:30 a.m. to 4:30 p.m.

Location: Corporate Bldg., conference room 020B, 9200 Corporate Blvd., Rockville, MD.

Contact Person: John C. Monahan, Center for Devices and Radiological Health (HFZ-470), Food and Drug Administration, 9200 Corporate Blvd., Rockville, MD 20850, 301-594-1212, or FDA Advisory Committee Information Line, 1-800-741-8138 (301-443-0572 in the Washington, DC area), code 12526. Please call the Information Line for up-to-date information on this meeting.

Agenda: The committee will discuss general issues and make recommendations concerning an original premarket approval application for an ultrasound bone density device.

Procedure: Interested persons may present data, information, or views, orally or in writing, on issues pending before the committee. Written submissions may be made to the contact person by August 11, 1997. Oral presentations from the public will be scheduled between approximately 9:45 a.m. and 10:45 a.m. Time allotted for each presentation may be limited. Those desiring to make formal oral presentations should notify the contact person before August 11, 1997, and submit a brief statement of the general nature of the evidence or arguments they wish to present, the names and addresses of proposed participants, and an indication of the approximate time requested to make their presentation.

Notice of this meeting is given under the Federal Advisory Committee Act (5 U.S.C. app. 2).

Dated: July 7, 1997.

Michael A. Friedman,

Deputy Commissioner for Operations.

[FR Doc. 97-18213 Filed 7-10-97; 8:45 am]

BILLING CODE 4160-01-F

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Health Resources and Services Administration

Agency Information Collection Activities: Submission for OMB Review; Comment Request

Periodically, the Health Resources and Services Administration (HRSA) publishes abstracts of information collection requests under review by the Office of Management and Budget, in compliance with the Paperwork Reduction Act of 1995 (44 U.S.C. Chapter 35). To request a copy of the clearance requests submitted to OMB for review, call the HRSA Reports Clearance Officer on (301)-443-1129.

The following request has been submitted to the Office of Management and Budget for review under the Paperwork Reduction Act of 1995:

Proposed Project: Area Health Education Centers (AHEC) and Health Education Training Centers (HETC): Managed Care Inventory Project—New—Section 746(a) of the Public Health Service Act authorizes Federal assistance to schools of medicine (allopathic and osteopathic) which have cooperative arrangements with one or more public or nonprofit private area health education centers (AHECs) for the planning, development and operation of area health education center programs. Section 746(f) of the PHS Act authorizes Federal assistance to schools of allopathic and osteopathic medicine, or parent institutions on behalf of such schools, or a consortium of such schools to plan, develop, establish, maintain or operate HETCs. The support is designed to improve the supply, distribution, quality, and efficiency of (a) personnel providing health services in the State of Florida or along the border between the United States and Mexico and (b) personnel providing, in other urban and rural areas of the U.S., health services to any population group, including Hispanic individuals and recent refugees, that have demonstrated serious health care needs. Program support is also used to encourage health promotion and disease prevention through public education.

A telephone survey is proposed of federally funded AHEC and HETC programs to determine the variety and

Marion Merrell Dow—Cont.

Treatment

The airway should be secured and adequate respiratory exchange should be established in cases of overdosage with RIFATER.

Obtain blood samples for immediate determination of gases, electrolytes, BUN, glucose, etc; type and cross-match blood in preparation for possible hemodialysis.

Gastric lavage within the first 2 to 3 hours after ingestion is advised, but it should not be attempted until convulsions are under control. To treat convulsions, administer IV diazepam or short-acting barbiturates, and IV pyridoxine (usually 1 mg/1 mg isoniazid ingested). Following evacuation of gastric contents, the instillation of activated charcoal slurry into the stomach may help absorb any remaining drug from the gastrointestinal tract. Antiemetic medication may be required to control severe nausea and vomiting.

RAPID CONTROL OF METABOLIC ACIDOSIS IS FUNDAMENTAL TO MANAGEMENT. Give IV sodium bicarbonate at once and repeat as needed, adjusting subsequent dosage on the basis of laboratory findings (ie, serum sodium, pH, etc).

Forced osmotic diuresis must be started early and should be continued for some hours after clinical improvement to hasten renal clearance of drug and help prevent relapse; monitor fluid intake and output.

Hemodialysis is advised for severe cases; if this is not available, peritoneal dialysis can be used along with forced diuresis.

Along with measures based on initial and repeated determination of blood gases and other laboratory tests as needed, utilize meticulous respiratory and other intensive care to protect against hypoxia, hypotension, aspiration pneumonitis, etc.

DOSAGE AND ADMINISTRATION

Adults: Patients should be given the following single daily dose of RIFATER either 1 hour before or 2 hours after a meal with a full glass of water.

Patients weighing ≤ 44 kg—4 tablets

Patients weighing between 45–54 kg—5 tablets

Patients weighing ≥ 55 kg—6 tablets

Children: The ratio of the drugs in RIFATER may not be appropriate in children or adolescents under the age of 15 (eg, higher mg/kg doses of isoniazid are usually given in children than adults).

RIFATER is recommended in the initial phase of short-course therapy which is usually continued for 2 months. The Advisory Council for the Elimination of Tuberculosis, the American Thoracic Society, and the Centers for Disease Control and Prevention recommend that either streptomycin or ethambutol be added as a fourth drug in a regimen containing isoniazid (INH), rifampin and pyrazinamide for initial treatment of tuberculosis unless the likelihood of INH or rifampin resistance is very low. The need for a fourth drug should be reassessed when the results of susceptibility testing are known. If community rates of INH resistance are currently less than 4%, an initial treatment regimen with less than four drugs may be considered.

Following the initial phase, treatment should be continued with rifampin and isoniazid (eg, RIFAMATE®) for at least 4 months. Treatment should be continued for longer if the patient is still sputum or culture positive, if resistant organisms are present, or if the patient is HIV positive.

Concomitant administration of pyridoxine (B_6) is recommended in the malnourished, in those predisposed to neuropathy (eg, alcoholics and diabetics), and in adolescents.

See CLINICAL PHARMACOLOGY: General for dosing information in patients with renal failure.

HOW SUPPLIED

RIFATER tablets are light beige, smooth, round, and shiny sugar-coated tablets imprinted with "RIFATER" in black ink and contain 120 mg rifampin, 50 mg isoniazid, and 300 mg pyrazinamide, and are supplied as:

Bottles of 60 tablets (NDC 0088-0576-41).

Unit dose blister packages of 100 tablets (NDC 0088-0576-49).

Storage Conditions: Store at controlled room temperature 59–86°F (15–30°C). Protect from excessive humidity.

Reference: 1. National Committee for Clinical Laboratory Standards. 1990. Antimycobacterial Susceptibility Testing (Proposed Standard). Document M24-P.

Prescribing information as of June 1994

Mfd by Gruppo Lepetit, S.p.A.
20020 Lainate, Italy, for
Marion Merrell Dow Inc.
Kansas City, MO 64114

Shown in Product Identification Guide, page 322

SELDANE®

[sĕl 'dān]
(terfenadine)
60 mg Tablets

WARNING BOX
QT INTERVAL PROLONGATION/VENTRICULAR ARRHYTHMIA

RARE CASES OF SERIOUS CARDIOVASCULAR ADVERSE EVENTS, INCLUDING DEATH, CARDIAC ARREST, TORSADES DE POINTES, AND OTHER VENTRICULAR ARRHYTHMIAS, HAVE BEEN OBSERVED IN THE FOLLOWING CLINICAL SETTINGS, FREQUENTLY IN ASSOCIATION WITH INCREASED TERFENADINE LEVELS WHICH LEAD TO ELECTROCARDIOGRAPHIC QT PROLONGATION:

1. **CONCOMITANT ADMINISTRATION OF KETOCONAZOLE (NIZORAL) OR ITRACONAZOLE (SPORANOX)**
2. **OVERDOSE, INCLUDING SINGLE DOSES AS LOW AS 360 MG**
3. **CONCOMITANT ADMINISTRATION OF CLARITHROMYCIN, ERYTHROMYCIN, OR TROLEANDOMYCIN**
4. **SIGNIFICANT HEPATIC DYSFUNCTION**

TERFENADINE IS CONTRAINDICATED IN PATIENTS TAKING KETOCONAZOLE, ITRACONAZOLE, ERYTHROMYCIN, CLARITHROMYCIN, OR TROLEANDOMYCIN, AND IN PATIENTS WITH SIGNIFICANT HEPATIC DYSFUNCTION.

DO NOT EXCEED RECOMMENDED DOSE.

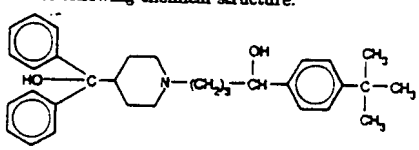
IN SOME CASES, SEVERE ARRHYTHMIAS HAVE BEEN PRECEDED BY EPISODES OF SYNCOPE. SYNCOPE IN PATIENTS RECEIVING TERFENADINE SHOULD LEAD TO DISCONTINUATION OF TREATMENT AND FULL EVALUATION OF POTENTIAL ARRHYTHMIAS.

(See CONTRAINDICATIONS, WARNINGS, CLINICAL PHARMACOLOGY, AND PRECAUTIONS: DRUG INTERACTIONS.)

DESCRIPTION

SELDANE (terfenadine) is available as tablets for oral administration. Each tablet contains 60 mg terfenadine. Tablets also contain, as inactive ingredients: corn starch, gelatin, lactose, magnesium stearate, and sodium bicarbonate.

Terfenadine is a histamine H_1-receptor antagonist with the chemical name α-[4-(1,1-Dimethylethyl) phenyl]-4-(hydroxydiphenylmethyl)-1-piperidinebutanol (±). The molecular weight is 471.68. The molecular formula is $C_{32}H_{41}NO_2$. It has the following chemical structure:



Terfenadine occurs as a white to off-white crystalline powder. It is freely soluble in chloroform, soluble in ethanol, and very slightly soluble in water.

CLINICAL PHARMACOLOGY

Terfenadine is chemically distinct from other antihistamines.

Histamine skin wheal studies have shown that SELDANE in single and repeated doses of 60 mg in 64 subjects has an antihistaminic effect beginning at 1–2 hours, reaching its maximum at 3–4 hours, and lasting in excess of 12 hours. The correlation between response on skin wheal testing and clinical efficacy is unclear. The four best controlled and largest clinical trials each lasted 7 days and involved about 1,000 total patients in comparisons of SELDANE (60 mg b.i.d.) with an active drug (chlorpheniramine, 4 mg t.i.d.; dexchlorpheniramine, 2 mg t.i.d.; or clemastine 1 mg b.i.d.). About 50–70% of SELDANE or other antihistamine recipients had moderate to complete relief of symptoms, compared with 30–50% of placebo recipients. The frequency of drowsiness with SELDANE was similar to the frequency with placebo and less than with other antihistamines. None of these studies showed a difference between SELDANE and other antihistamines in the frequency of anticholinergic effects. In studies which included 52 subjects in whom EEG assessments were made, no depressant effects have been observed.

Animal studies have demonstrated that terfenadine is a histamine H_1-receptor antagonist. In these animal studies, no sedative or anticholinergic effects were observed at effective antihistaminic doses. Radioactive disposition and autoradiographic studies in rats and radioligand binding studies with guinea pig brain H_1-receptors indicate that, at effective antihistamine doses, neither terfenadine nor its metabolites penetrate the blood brain barrier well.

On the basis of a mass balance study using ^{14}C labeled terfenadine the oral absorption of terfenadine was estimated to be at least 70%. Terfenadine itself undergoes extensive (99%) first pass metabolism to two primary metabolites, an active acid metabolite and an inactive dealkylated metabolite. Therefore, systemic availability of terfenadine is low under normal conditions, and parent terfenadine is not normally detectable in plasma at levels > 10 ng/mL. Although in rare cases there was measurable plasma terfenadine in apparently normal individuals without identifiable risk factors, the implications of this finding with respect to the variability of terfenadine metabolism in the normal population cannot be assessed without further study. Further studies of terfenadine metabolism in the general population are pending. From information gained in the ^{14}C study it appears that approximately forty percent of the total dose is eliminated renally (40% as acid metabolite, 30% dealkyl metabolite and 30% minor unidentified metabolites). Sixty percent of the dose is eliminated in the feces (50% as the acid metabolite, 2% unchanged terfenadine, and the remainder as minor unidentified metabolites). Studies investigating the effect of hepatic and renal insufficiency on the metabolism and excretion of terfenadine are incomplete. Preliminary information indicates that in cases of hepatic impairment, significant concentrations of unchanged terfenadine can be detected with the rate of acid metabolite formation being decreased. A single-dose study in patients with hepatic impairment revealed increased parent terfenadine and impaired metabolism, suggesting that additional drug accumulation may occur after repetitive dosing in such patients. Terfenadine is contraindicated for use in patients with significant hepatic dysfunction. (See CONTRAINDICATIONS and WARNINGS.) In subjects with normal hepatic function, unchanged terfenadine plasma concentrations have not been detected. **Elevated levels of parent terfenadine, whether due to significant hepatic dysfunction, concomitant medications, or overdose, have been associated with QT interval prolongation and serious cardiac adverse events.** (See CONTRAINDICATIONS and WARNINGS.) In controlled clinical trials in otherwise normal patients with rhinitis, small increases in QTc interval were observed at doses of 60 mg b.i.d. In studies at 300 mg b.i.d. a mean increase in QTc of 10% (range −4% to +30%) (mean increase of 46 msec) was observed.

Data have been reported demonstrating that compared to young subjects, elderly subjects experience a 25% reduction in clearance of the acid metabolite after single-dose oral administration of 120 mg. Further studies are necessary to fully characterize pharmacokinetics in the elderly.

In vitro studies demonstrate that terfenadine is extensively (97%) bound to human serum protein while the acid metabolite is approximately 70% bound to human serum protein. Based on data gathered from in vitro models of antihistaminic activity, the acid metabolite of terfenadine has approximately 30% of the H_1 blocking activity of terfenadine. The relative contribution of terfenadine and the acid metabolite to the pharmacodynamic effects have not been clearly defined. Since unchanged terfenadine is usually not detected in plasma, and active acid metabolite concentrations are relatively high, the acid metabolite may be the entity responsible for the majority of efficacy after oral administration of terfenadine.

In a study involving the administration of a single 60 mg SELDANE tablet to 24 subjects, mean peak plasma levels of the acid metabolite were 263 ng/mL (range 133–423 ng/mL) and occurred approximately 2.5 hours after dosing. Plasma concentrations of unchanged terfenadine were not detected. The elimination profile of the acid metabolite was biphasic in nature with an initial mean plasma half-life of 3.5 hours followed by a mean plasma half-life of 8 hours. Ninety percent of the plasma level time curve was associated with these half-lives. Although the elimination profile is somewhat complex, the effective pharmacokinetic half-life can be estimated at approximately 3.5 hours. However, receptor binding and pharmacologic effects, both therapeutic and adverse, may persist well beyond that time.

INDICATIONS AND USAGE

SELDANE is indicated for the relief of symptoms associated with seasonal allergic rhinitis such as sneezing, rhinorrhea, pruritus, and lacrimation.

Clinical studies conducted to date have not demonstrated effectiveness of terfenadine in the common cold.

CONTRAINDICATIONS

CONCOMITANT ADMINISTRATION OF TERFENADINE WITH KETOCONAZOLE (NIZORAL) OR ITRACONAZOLE (SPORANOX) IS CONTRAINDICATED. TERFENADINE IS ALSO CONTRAINDICATED IN PATIENTS WITH DISEASE STATES OR OTHER CONCOMITANT MEDICATIONS KNOWN TO IMPAIR ITS METABOLISM, INCLUDING SIGNIFICANT HEPATIC DYSFUNCTION, AND CONCURRENT USE OF CLARITHROMYCIN, ERYTHROMYCIN, OR TROLEANDOMYCIN. QT PROLONGATION HAS BEEN DEMONSTRATED IN SOME PATIENTS TAKING TERFENADINE IN THESE SETTINGS, AND RARE CASES OF SERIOUS CARDIOVASCULAR EVENTS, IN-

CLUDING DEATH, CARDIAC ARREST, AND TORSADES DE POINTES, HAVE BEEN REPORTED IN THESE PATIENT POPULATIONS. (See WARNINGS and PRECAUTIONS: Drug Interactions.)

SELDANE is contraindicated in patients with a known hypersensitivity to terfenadine or any of its ingredients.

WARNINGS

Terfenadine undergoes extensive metabolism in the liver by a specific cytochrome P-450 isoenzyme. This metabolic pathway may be impaired in patients with hepatic dysfunction (alcoholic cirrhosis, hepatitis) or who are taking drugs such as ketoconazole, itraconazole, or clarithromycin, erythromycin, or troleandomycin (macrolide antibiotics), or other potent inhibitors of this isoenzyme. Interference with this metabolism can lead to elevated terfenadine plasma levels associated with QT prolongation and increased risk of ventricular tachyarrhythmias (such as torsades de pointes, ventricular tachycardia, and ventricular fibrillation) at the recommended dose. SELDANE is contraindicated for use by patients with these conditions (see WARNING BOX, CONTRAINDICATIONS, and PRECAUTIONS: Drug Interactions).

Other patients who may be at risk for these adverse cardiovascular events include patients who may experience new or increased QT prolongation while receiving certain drugs or having conditions which lead to QT prolongation. These include patients taking certain antiarrhythmics, bepridil, certain psychotropics, probucol, or astemizole; patients with electrolyte abnormalities such as hypokalemia or hypomagnesemia, or taking diuretics with potential for inducing electrolyte abnormalities; and patients with congenital QT syndrome. SELDANE is not recommended for use by patients with these conditions.

The relationship of underlying cardiac disease to the development of ventricular tachyarrhythmias while on SELDANE therapy is unclear; nonetheless, SELDANE should also be used with caution in these patients.

PRECAUTIONS

Information for Patients

Patients taking SELDANE should receive the following information and instructions. Antihistamines are prescribed to reduce allergic symptoms. Patients should be advised to take SELDANE only as needed and NOT TO EXCEED THE PRESCRIBED DOSE. Patients should be questioned about use of any other prescription or over-the-counter medication, and should be cautioned regarding the potential for life-threatening arrhythmias with concurrent use of ketoconazole, itraconazole, clarithromycin, erythromycin, or troleandomycin. Patients should be advised to consult the physician before concurrent use of other medications with terfenadine. Patients should be questioned about pregnancy or lactation before starting SELDANE therapy, since the drug should be used in pregnancy or lactation only if the potential benefit justifies the potential risk to fetus or baby. Patients should also be instructed to store this medication in a tightly closed container in a cool, dry place, away from heat or direct sunlight, and away from children.

Drug Interactions

Ketoconazole

Spontaneous adverse reaction reports of patients taking concomitant ketoconazole with recommended doses of terfenadine demonstrate QT interval prolongation and rare serious cardiac events, e.g. death, cardiac arrest, and ventricular arrhythmia including torsades de pointes. Pharmacokinetic data indicate that ketoconazole markedly inhibits the metabolism of terfenadine, resulting in elevated plasma terfenadine levels. Presence of unchanged terfenadine is associated with statistically significant prolongation of the QT and QTc intervals. **Concomitant administration of ketoconazole and terfenadine is contraindicated** (see CONTRAINDICATIONS, WARNINGS, and ADVERSE REACTIONS).

Itraconazole

Torsades de pointes and elevated parent terfenadine levels have been reported during concomitant use of terfenadine and itraconazole in clinical trials of itraconazole and from foreign post-marketing sources. One death has also been reported from foreign post-marketing sources. **Concomitant administration of itraconazole and terfenadine is contraindicated** (see CONTRAINDICATIONS, WARNINGS and ADVERSE REACTIONS).

Due to the chemical similarity of other azole-type antifungal agents (including fluconazole, metronidazole, and miconazole) to ketoconazole and itraconazole, concomitant use of these products with terfenadine is not recommended pending full examination of potential interactions.

Macrolides

Clinical drug interaction studies indicate that erythromycin and clarithromycin can exert an effect on terfenadine metabolism by a mechanism which may be similar to that of ketoconazole, but to lesser extent. Although erythromycin [illegible] increases the clearance of the terfenadine acid [illegible] its influence on terfenadine plasma levels is still [illegible]. A few spontaneous accounts of QT interval prolongation with ventricular arrhythmia, including torsades de pointes, have been reported in patients receiving erythromycin or troleandomycin.

Concomitant administration of terfenadine with clarithromycin, erythromycin, or troleandomycin is contraindicated (see CONTRAINDICATIONS, WARNINGS, and ADVERSE REACTIONS). Pending full characterization of potential interactions, concomitant administration of terfenadine with other macrolide antibiotics, including azithromycin, is not recommended. Studies to evaluate the potential interaction of terfenadine with azithromycin are in progress.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Oral doses of terfenadine, corresponding to 63 times the recommended human daily dose, in mice for 18 months or in rats for 24 months, revealed no evidence of tumorigenicity. Microbial and micronucleus test assays with terfenadine have revealed no evidence of mutagenesis.

Reproduction and fertility studies in rats showed no effects on male or female fertility at oral doses of up to 21 times the human daily dose. At 63 times the human daily dose there was a small but significant reduction in implants and at 125 times the human daily dose reduced implants and increased post-implantation losses were observed, which were judged to be secondary to maternal toxicity.

Pregnancy Category C

There was no evidence of animal teratogenicity. Reproduction studies have been performed in rats at doses 63 times and 125 times the human daily dose and have revealed decreased pup weight gain and survival when terfenadine was administered throughout pregnancy and lactation. There are no adequate and well-controlled studies in pregnant women. SELDANE should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects

SELDANE is not recommended for nursing women. The drug has caused decreased pup weight gain and survival in rats given doses 63 times and 125 times the human daily dose throughout pregnancy and lactation. Effects on pups exposed to SELDANE only during lactation are not known, and there are no adequate and well-controlled studies in women during lactation.

Pediatric Use

Safety and effectiveness of SELDANE in pediatric patients below the age of 12 years have not been established.

ADVERSE REACTIONS

Cardiovascular Adverse Events

Rare reports of severe cardiovascular adverse effects have been received which include ventricular tachyarrhythmias (torsades de pointes, ventricular tachycardia, ventricular fibrillation, and cardiac arrest), hypotension, palpitations, syncope, and dizziness. Rare reports of deaths resulting from ventricular tachyarrhythmias have been received (see CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS: Drug Interactions). Hypotension, palpitations, syncope, and dizziness could reflect undetected ventricular arrhythmia. IN SOME PATIENTS, DEATH, CARDIAC ARREST, OR TORSADES DE POINTES HAVE BEEN PRECEDED BY EPISODES OF SYNCOPE. (See WARNING BOX.) Rare reports of serious cardiovascular adverse events have been received, some involving QT prolongation and torsades de pointes, in apparently normal individuals without identifiable risk factors; there is not conclusive evidence of a causal relationship of these events with terfenadine. Although in rare cases there was measurable plasma terfenadine, the implications of this finding with respect to the variability of terfenadine metabolism in the normal population cannot be assessed without further study. In controlled clinical trials in otherwise normal patients with rhinitis, small increases in QTc interval were observed at doses of 60 mg b.i.d. In studies at 300 mg b.i.d. a mean increase in QTc of 10% (range −4% to +30%) (mean increase of 46 msec) was observed.

General Adverse Events

Experience from clinical studies, including both controlled and uncontrolled studies involving more than 2,400 patients who received SELDANE, provides information on adverse experience incidence for periods of a few days up to six months. The usual dose in these studies was 60 mg twice daily, but in a small number of patients, the dose was as low as 20 mg twice a day, or as high as 600 mg daily.

In controlled clinical studies using the recommended dose of 60 mg b.i.d., the incidence of reported adverse effects in patients receiving SELDANE was similar to that reported in patients receiving placebo.

[See table above.]

In addition to the more frequent side effects reported in clinical trials (See Table), adverse effects have been reported at a lower incidence in clinical trials and/or spontaneously during marketing of SELDANE that warrant listing as possibly associated with drug administration. These include: alopecia (hair loss or thinning), anaphylaxis, angioedema, bronchospasm, confusion, depression, galactorrhea, insomnia, menstrual disorders (including dysmenorrhea), musculoskeletal symptoms, nightmares, paresthesia, photosensitivity, rapid flare of psoriasis, seizures, sinus tachycardia, sweating, thrombocytopenia, tremor, urinary frequency, and visual disturbances.

In clinical trials, several instances of mild, or in one case, moderate transaminase elevations were seen in patients receiving SELDANE. Mild elevations were also seen in placebo treated patients. Marketing experiences include isolated reports of jaundice, cholestatic hepatitis, and hepatitis. In most cases available information is incomplete.

ADVERSE EVENTS REPORTED IN CLINICAL TRIALS

	Percent of Patients Reporting				
	Controlled Studies*			All Clinical Studies**	
Adverse Event	SELDANE n = 781	Placebo n = 665	Control n = 626***	SELDANE n = 2462	Placebo n = 1478
Central Nervous System					
Drowsiness	9.0	8.1	18.1	8.5	8.2
Headache	6.3	7.4	3.8	15.8	11.2
Fatigue	2.9	0.9	5.8	4.5	3.0
Dizziness	1.4	1.1	1.0	1.5	1.2
Nervousness	0.9	0.2	0.6	1.7	1.0
Weakness	0.9	0.6	0.2	0.6	0.5
Appetite Increase	0.6	0.0	0.0	0.5	0.0
Gastrointestinal System					
Gastrointestinal Distress (Abdominal distress, Nausea, Vomiting, Change in bowel habits)	4.6	3.0	2.7	7.6	5.4
Eye, Ear, Nose, and Throat					
Dry Mouth/Nose/Throat	2.3	1.8	3.5	4.8	3.1
Cough	0.9	0.2	0.5	2.5	1.7
Sore Throat	0.5	0.3	0.5	3.2	1.6
Epistaxis	0.0	0.8	0.2	0.7	0.4
Skin					
Eruption (including rash and urticaria) or itching	1.0	1.7	1.4	1.6	2.0

* Duration of treatment in "CONTROLLED STUDIES" was usually 7–14 days.
** Duration of treatment in "ALL CLINICAL STUDIES" was up to 6 months.
*** CONTROLLED DRUGS: Chlorpheniramine (291 patients), d-Chlorpheniramine (189 patients), Clemastine (146 patients)

OVERDOSAGE

Signs and symptoms of overdosage may be absent or mild (e.g. headache, nausea, confusion); but adverse cardiac events including cardiac arrest, ventricular arrhythmias including torsades de pointes and QT prolongation have been reported at overdoses of 360 mg or more and occur more frequently at doses in excess of 600 mg, and QTc prolongations of up to 30% have been observed at a dose of 300 mg b.i.d. Seizures and syncope have also been reported. USE OF DOSES IN EXCESS OF 60 MG B.I.D. IS NOT RECOMMENDED. (See WARNING BOX, CLINICAL PHARMACOLOGY, and ADVERSE REACTIONS.)

In overdose cases, where ventricular arrhythmias are associated with significant QTc prolongation, treatment with antiarrhythmics known to prolong QTc intervals is not recommended

Continued on next page

Marion Merrell Dow—Cont.

Therefore, in cases of overdosage, cardiac monitoring for at least 24 hours is recommended and for as long as QTc is prolonged, along with standard measures to remove any unabsorbed drug. Limited experience with the use of hemoperfusion (n = 1) or hemodialysis (n = 3) was not successful in completely removing the acid metabolite of terfenadine from the blood.

Treatment of the signs and symptoms of overdosage should be symptomatic and supportive after the acute stage.

Oral LD_{50} values for terfenadine were greater than 5000 mg/kg in mature mice and rats. The oral LD_{50} was 438 mg/kg in newborn rats.

DOSAGE AND ADMINISTRATION

One tablet (60 mg) twice daily for adults and children 12 years and older.

USE OF DOSES IN EXCESS OF 60 MG B.I.D. IS NOT RECOMMENDED BECAUSE OF THE INCREASED POTENTIAL FOR QT INTERVAL PROLONGATION AND ADVERSE CARDIAC EVENTS. (See WARNING BOX.)

USE OF TERFENADINE IN PATIENTS WITH SIGNIFICANT HEPATIC DYSFUNCTION AND IN PATIENTS TAKING KETOCONAZOLE, ITRACONAZOLE, CLARITHROMYCIN, ERYTHROMYCIN, OR TROLEANDOMYCIN IS CONTRAINDICATED. (See CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS: Drug Interactions.)

HOW SUPPLIED

NDC 0068-0723-61
60 mg tablets in bottles of 100.
NDC 0068-0723-65
60 mg tablets in bottles of 500.
Tablets are round, white, and debossed "SELDANE". Store tablets at controlled room temperature (59–86°F) (15–30°C). Protect from exposure to temperatures above 104°F (40°C) and moisture.

Prescribing information as of January 1995
Merrell Dow Pharmaceuticals Inc.
Subsidiary of Marion Merrell Dow Inc.
Kansas City, MO 64114
U.S. Patents 3,878,217; 4,254,129.
Other patent applications pending.

PATIENT INFORMATION
SELDANE®
Generic name
terfenadine (ter-FEN-a-deen)
60 mg Tablets

This leaflet is a summary of important information about SELDANE. Be sure to ask your doctor if you have any questions or want to know more.

What is SELDANE and What is It Used For?

SELDANE is an antihistamine. It is used to relieve symptoms of seasonal allergies or hay fever. These symptoms include runny nose, sneezing, itching of the nose or throat, and itchy, watery eyes.

Clinical studies conducted to date with SELDANE have not demonstrated effectiveness in relieving the symptoms of the common cold.

How Do I Take SELDANE?

- Take SELDANE only as needed when you have symptoms of seasonal allergy or hay fever.
- The recommended dose of SELDANE is one tablet taken twice a day. **DO NOT TAKE MORE OFTEN THAN ONE TABLET EVERY TWELVE HOURS**
- Follow any other instructions your doctor gives you.

What Are The Important Warnings About Using SELDANE?

WARNING: DO NOT USE SELDANE IF YOU ARE USING KETOCONAZOLE (NIZORAL), ITRACONAZOLE (SPORANOX), ERYTHROMYCIN, CLARITHROMYCIN (BIAXIN), OR TROLEANDOMYCIN (TAO). IF YOU HAVE ANY LIVER OR HEART PROBLEMS, TALK TO YOUR DOCTOR BEFORE YOU USE SELDANE.

Do not use SELDANE with any other prescription or nonprescription medicines without first talking to your doctor and pharmacist.

If you faint, become dizzy, have any unusual heartbeats, or any other unusual symptoms while using SELDANE, contact your doctor.

If you become pregnant or are nursing a baby, talk to your doctor about whether you should take SELDANE. Your doctor will decide whether you should take SELDANE based on the benefits and the risks.

What Are the Risks of Using SELDANE?

The side effects which occur most often are headaches and mild stomach or intestinal problems.

In rare cases, SELDANE has caused **IRREGULAR HEARTBEATS** which may cause serious problems like fainting, dizziness, cardiac arrest, or death. In these rare cases, this occurred when SELDANE was taken:

- in more than the recommended dose (remember, do not take more often than one tablet every twelve hours.);
- with the antifungal drugs ketoconazole (Nizoral) or itraconazole (Sporanox);
- with the antibiotic drugs erythromycin, clarithromycin (Biaxin), or troleandomycin (TAO);
- by patients with serious liver disease.

How Do I Store SELDANE?

SELDANE should be stored in a tightly closed container, in a cool place, out of direct sunlight. It should be kept away from children.

Patient Information as of January 1995

Shown in Product Identification Guide, page 322

SELDANE-D® Ⓡ

[sĕl 'dān dee]
(terfenadine and pseudoephedrine hydrochloride)
Extended-Release Tablets

WARNING BOX
QT INTERVAL PROLONGATION/VENTRICULAR ARRHYTHMIA

RARE CASES OF SERIOUS CARDIOVASCULAR ADVERSE EVENTS, INCLUDING DEATH, CARDIAC ARREST, TORSADES DE POINTES, AND OTHER VENTRICULAR ARRHYTHMIAS, HAVE BEEN OBSERVED IN THE FOLLOWING CLINICAL SETTINGS, FREQUENTLY IN ASSOCIATION WITH INCREASED TERFENADINE LEVELS WHICH LEAD TO ELECTROCARDIOGRAPHIC QT PROLONGATION:

1. **CONCOMITANT ADMINISTRATION OF KETOCONAZOLE (NIZORAL) OR ITRACONAZOLE (SPORANOX)**
2. **OVERDOSE, INCLUDING SINGLE TERFENADINE DOSES AS LOW AS 360 MG**
3. **CONCOMITANT ADMINISTRATION OF CLARITHROMYCIN, ERYTHROMYCIN, OR TROLEANDOMYCIN**
4. **SIGNIFICANT HEPATIC DYSFUNCTION**

TERFENADINE IS CONTRAINDICATED IN PATIENTS TAKING KETOCONAZOLE, ITRACONAZOLE, ERYTHROMYCIN, CLARITHROMYCIN, OR TROLEANDOMYCIN, AND IN PATIENTS WITH SIGNIFICANT HEPATIC DYSFUNCTION.

DO NOT EXCEED RECOMMENDED DOSE.

IN SOME CASES, SEVERE ARRHYTHMIAS HAVE BEEN PRECEDED BY EPISODES OF SYNCOPE. SYNCOPE IN PATIENTS RECEIVING TERFENADINE SHOULD LEAD TO DISCONTINUATION OF TREATMENT AND FULL EVALUATION OF POTENTIAL ARRHYTHMIAS.

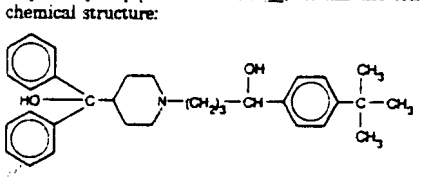
(See CONTRAINDICATIONS, WARNINGS, CLINICAL PHARMACOLOGY, AND PRECAUTIONS: DRUG INTERACTIONS.)

DESCRIPTION

SELDANE-D (terfenadine and pseudoephedrine hydrochloride) Extended-Release Tablets are available for oral administration.

Each tablet contains 60 mg terfenadine and 10 mg of pseudoephedrine hydrochloride in an outer press-coat for immediate release and 110 mg pseudoephedrine hydrochloride in an extended-release core. Tablets also contain, as inactive ingredients: colloidal silicon dioxide, ethylcellulose, glycerin, hydroxypropyl cellulose, hydroxypropyl methylcellulose 2208, hydroxypropyl methylcellulose 2910, lactose, magnesium stearate, microcrystalline cellulose, polysorbate 80, precipitated calcium carbonate, pregelatinized corn starch, sodium lauryl sulfate, sodium starch glycolate, talc, titanium dioxide, and zinc stearate.

Terfenadine is a histamine H_1-receptor antagonist with the chemical name α-[4-(1,1-Dimethylethyl)phenyl]-4-(hydroxydiphenylmethyl)-1-piperidinebutanol(±). It has the following chemical structure:



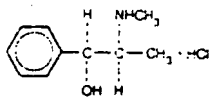
The molecular weight is 471.68. The molecular formula is $C_{32}H_{41}NO_2$.

Terfenadine occurs as a white to off-white crystalline powder. It is freely soluble in chloroform, soluble in ethanol, and very slightly soluble in water.

Pseudoephedrine hydrochloride is an adrenergic (vasoconstrictor) agent with the chemical name [S-(R*,R*)]-α-[1-(methylamino)ethyl]-benzenemethanol hydrocholoride. It has the following chemical structure:

[See chemical structure at top of next column.]

The molecular weight is 201.70. The molecular formula is $C_{10}H_{15}NO \cdot HCl$.



Pseudoephedrine hydrochloride occurs as fine, white to off-white crystals or powder, having a faint characteristic odor. It is very soluble in water, freely soluble in alcohol, and sparingly soluble in chloroform.

CLINICAL PHARMACOLOGY

Terfenadine, a histamine H_1-receptor antagonist, is chemically distinct from other antihistamines.

Histamine skin wheal studies have shown that terfenadine in single and repeated doses of 60 mg in 64 subjects has an antihistaminic effect beginning at 1–2 hours, reaching its maximum at 3–4 hours, and lasting in excess of 12 hours. The correlation between response on skin wheal testing and clinical efficacy is unclear.

The four best controlled and largest clinical trials of Seldane each lasted 7 days and involved about 1,000 total patients in comparisons of Seldane (60 mg b.i.d.) with an active drug (chlorpheniramine, 4 mg t.i.d.; dexchlorpheniramine, 2 mg t.i.d.; or clemastine 1 mg b.i.d.). About 50–70% of Seldane or other antihistamine recipients had moderate to complete relief of symptoms, compared with 30–50% of placebo recipients. The frequency of drowsiness with Seldane was similar to the frequency with placebo and less than with other antihistamines. In studies which included 52 subjects in whom EEG assessments were made, no depressant effects have been observed. SELDANE-D has not been studied for effectiveness in relieving the symptoms of the common cold.

Animal studies have demonstrated that terfenadine is a histamine H_1-receptor antagonist. In these animal studies, no sedative or anticholinergic effects were observed at effective antihistaminic doses. Radioactive disposition and autoradiographic studies in rats and radioligand binding studies with guinea pig brain H_1-receptors indicate that, at effective antihistamine doses, neither terfenadine nor its metabolites penetrate the blood brain barrier well.

On the basis of a mass balance study using ^{14}C labeled terfenadine the oral absorption of terfenadine was estimated to be at least 70%. Terfenadine itself undergoes extensive (99%) first pass metabolism to two primary metabolites, an active acid metabolite and an inactive dealkylated metabolite. Therefore, systemic availability of terfenadine is low under normal conditions, and parent terfenadine is not normally detectable in plasma at levels > 10 ng/mL. Although in rare cases there was measurable plasma terfenadine in apparently normal individuals without identifiable risk factors, the implications of this finding with respect to the variability of terfenadine metabolism in the normal population cannot be assessed without further study. Further studies of terfenadine metabolism in the general population are pending. From information gained in the ^{14}C study it appears that approximately forty percent of the total dose is eliminated renally (40% as acid metabolite, 30% dealkyl metabolite, and 30% minor unidentified metabolites). Sixty percent of the dose is eliminated in the feces (50% as the acid metabolite, 2% unchanged terfenadine, and the remainder as minor unidentified metabolites). Studies investigating the effect of hepatic and renal insufficiency on the metabolism and excretion of terfenadine are incomplete. Preliminary information indicates that in cases of hepatic impairment, significant concentrations of unchanged terfenadine can be detected with the rate of acid metabolite formation being decreased. A single-dose study in patients with hepatic impairment revealed increased parent terfenadine and impaired metabolism, suggesting that additional drug accumulation may occur after repetitive dosing in such patients. Terfenadine is contraindicated for use in patients with significant hepatic dysfunction. (See CONTRAINDICATIONS and WARNINGS.) In subjects with normal hepatic function, unchanged terfenadine plasma concentrations have not been detected. **Elevated levels of parent terfenadine, whether due to significant hepatic dysfunction, concomitant medications, or overdose, have been associated with QT interval prolongation and serious cardiac adverse events.** (See CONTRAINDICATIONS and WARNINGS.) In controlled clinical trials in otherwise normal patients with rhinitis, small increases in QTc interval were observed at doses of 60 mg b.i.d. In studies at 300 mg b.i.d. a mean increase in QTc of 10% (range −4% to +30%) (mean increase of 46 msec) was observed.

Data have been reported demonstrating that compared to young subjects, elderly subjects experience a 25% reduction in clearance of the acid metabolite after single-dose oral administration of 120 mg. Further studies are necessary to fully characterize pharmacokinetics in the elderly.

In vitro studies demonstrate that terfenadine is extensively (97%) bound to human serum protein while the acid metabolite is approximately 70% bound to human serum protein. Based on data gathered from in vitro models of antihistaminic activity, the acid metabolite of terfenadine has approximately 30% of the H_1-blocking activity of terfenadine. The relative contribution of terfenadine and the acid metabolite

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May 17, 1996

Dockets Management Branch
Food and Drug Administration
Room 1-23
12420 Parklawn Drive
Rockville, MD 20857

05-17-96P03:51 RCVD

Re: Citizen Petition -- Eligibility Of Fexofenadine For Five-Year Exclusivity

Dear Sir or Madam:

We respectfully submit this petition under 21 U.S.C. § 355 and 21 C.F.R. § 10.30, to request the Commissioner to declare that the approval of a new drug application (NDA) for the active metabolite of a previously approved active ingredient is not entitled to 5 year exclusivity under 21 U.S.C. §§ 355(c)(3)(D)(ii) and (j)(4)(D)(ii), and to refrain from granting such exclusivity to any NDA approved for fexofenadine (otherwise known as terfenadine acid metabolite and hereinafter referred to as TAM).

A. ACTION REQUESTED

We request that the Commissioner take the following actions:

(1) Declare that:

(a) Five year exclusivity under 21 U.S.C. §§ 355(c)(3)(D)(ii) and (j)(4)(D)(ii) is available only to new therapeutic moieties;

(b) Therapeutic moieties are molecular components that are responsible for the drug effect; and

(c) Metabolites of previously approved drugs are not entitled to 5 year exclusivity unless they are demonstrated to contain new therapeutic moieties.

(2) Publish a notice in the Federal Register stating this policy and declaring that the agency will follow this policy in all exclusivity determinations;

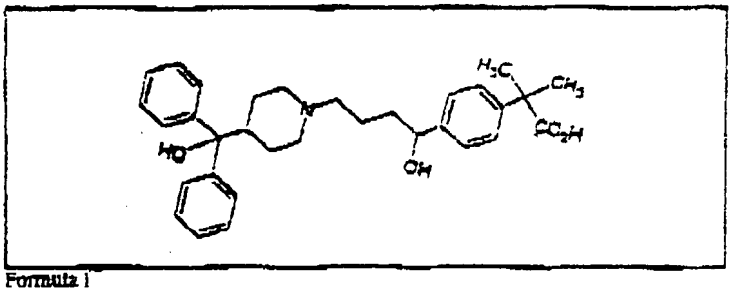
(3) Declare that TAM does not contain a new therapeutic moiety entitled to five-year exclusivity; and

(4) Refrain from granting five-year exclusivity to any NDA approved for TAM.

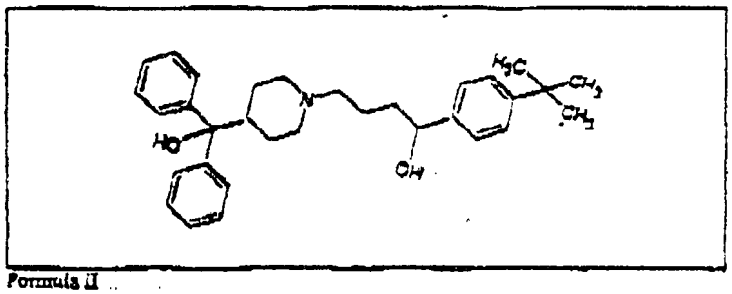
B. STATEMENT OF GROUNDS

1. THE THERAPEUTIC MOIETY IN TAM IS NOT NEW[1]

TAM (Formula I below) is a derivative of Terfenadine (Formula II below).



Formula I



Formula II

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[1] The scientific statements in this petition are based on our understanding and belief. We will supplement this petition in the near future with a declaration from an expert scientist to support these statements.

The TAM molecule is identical to the terfenadine molecule but for the presence in TAM of two oxygen atoms in place of two hydrogen atoms of terfenadine (see the starred carbon atom shown at the far right in Formulae I and II). Of the 84 atoms in terfenadine and TAM, only these two are different, while the other 82 are identical.

The substitution of oxygen in TAM for hydrogen of terfenadine is not responsible for, and has no known or likely effect on, the antihistaminic activity of TAM. Indeed, both active ingredients are effective antihistamines, with similar time to peak antihistaminic effect and duration of action. Moreover, their receptor selectivity and receptor specificity are the same: both are H_1-selective antagonists, both are free of muscarinic effects, neither is a beta agonist or beta antagonist, and both are non-anticholinergic. It is also significant that neither TAM nor terfenadine passes the blood-brain barrier and thus, both are characterized as non-sedating antihistamines.

The similarity in effectiveness between TAM and terfenadine is explained by the fact that terfenadine is said to undergo extensive (99%) and rapid first pass metabolism to form TAM and an inactive metabolite. See Seldane® package insert (Attachment A). Systemic availability of terfenadine is low; it is not normally detectable in plasma. As a result, in the labeling for terfenadine, the pharmacology of terfenadine is described by reference to TAM rather than by reference to terfenadine itself. See also FDA guidance document "Terfenadine Tablets In Vivo Bioequivalence and In Vitro Dissolution," dated June 12, 1992 (Attachment B). It is TAM pharmacokinetics, and not those of terfenadine, that are central to the determination of the proper dosing regimen of Seldane®. Given this, the rapid conversion and lack of systemic availability of terfenadine, and the related fact that TAM is the marker for determination of plasma levels of drug in connection with Seldane® administration, it is clear that the active moiety in Seldane® and TAM is the same. It would defy reason to consider TAM to be new after it has been intentionally dosed to Seldane® patients for many years.

The overwhelming structural and functional similarities between terfenadine and TAM make it clear that the antihistaminic activity of TAM is embodied in the same therapeutic moiety that is present in terfenadine. Just as clearly, this therapeutic moiety does not involve the starred carbon atom in Formulae I and II; rather, the antihistaminic activity of TAM resides in the 82 atoms that are common to terfenadine and TAM.

Thus, while TAM and terfenadine are different molecules, the difference is slight and ceases to exist as terfenadine is metabolized into TAM. The filer of the NDA for TAM has simply replaced one approved active ingredient with a closely related molecular derivative having the same therapeutic moiety and same effect at the site of drug action. While TAM, as a new active ingredient, may be entitled to three-year exclusivity if it represents a therapeutic gain and is

supported by new clinical studies, it is not a molecular innovation giving rise to five-year exclusivity.

2. FIVE-YEAR EXCLUSIVITY CAN BE AWARDED ONLY TO THERAPEUTIC MOIETIES THAT ARE ENTIRELY NEW

As the agency has stated its regulations and in numerous policy statements, five-year exclusivity is not available for every new active ingredient. The legislative history of the exclusivity provisions of the Federal Food, Drug, and Cosmetic Act ("the Act") make clear that five-year exclusivity is available only to new active ingredients that contain an "entirely new active moiety." 54 Fed. Reg. 28871, 28897-98 (1989). A moiety is a molecular component[2] and a given moiety may form part of many molecules. FDA uses the terms "active moiety" and "therapeutic moiety" interchangeably and has long defined the therapeutic moiety as the molecular structure "that actually achieves the intended effect in the diagnosis, cure, mitigation, treatment, or prevention of a disease or in affecting the structure or function of the human body." 49 Fed. Reg. 2932, 2937 (1980). FDA distinguishes therapeutic moieties from active ingredients as follows:

> [T]he same therapeutic moiety may appear in slightly different chemical forms, e.g., as different salts or esters of the same molecule. To distinguish these separate forms, the term "active drug ingredient" is used; each salt or ester of a therapeutic agent is a unique active drug ingredient.

Id. at 2937-38.

FDA's distinction between therapeutic moieties and active ingredients forms the basis for its interpretation of the applicability of five-year exclusivity. This interpretation is based on the wording of the statute as well as on the clear expression of congressional intent found in the legislative history. The statute provides five-year exclusivity for drugs that contain no previously approved "active ingredient (including any ester or salt of the active ingredient)." 21 U.S.C. §§ 355(c)(3)(D)(ii) and (j)(4)(D)(ii). Although this wording is somewhat ambiguous, it indicates clearly that five-year exclusivity is not intended for every new active ingredient. FDA's interprets the wording to require a determination of whether the active ingredient contains a therapeutic moiety

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[2] A moiety is a portion of a molecule. Dorland's Illustrated Medical Dictionary, 26th ed. (1985), p. 831.

that has not been previously approved. The agency explained this interpretation when it originally proposed its regulations governing exclusivity:

> FDA bases this interpretation on the statutory language and on the definition of a "new molecular entity" or "Type I" drug in FDA's IND/NDA classification scheme (which is used to classify new drugs by chemical type and therapeutic significance), which was in effect at the time the 1984 Amendments were under consideration in Congress. FDA's longstanding interpretation of the term "new molecular entity" is that it is a compound containing an entirely new active moiety.

54 Fed. Reg. at 28897-98. The agency further notes that this interpretation is required because "Congress . . . did not intend to confer significant periods of exclusivity for minor variations of previously approved chemical compounds." Id. at 28898.

The legislative history amply supports this interpretation. Five-year exclusivity is described in numerous instances as being intended for "new chemical entities" See, e.g., 130 Cong. Rec. 2445 (statement of Rep. Waxman, co-sponsor of legislation), 23765 (statement of Sen. Hatch, co-sponsor of legislation) (1984). Moreover, the House Committee Report describes identical statutory language found elsewhere in the 1984 Amendments as referring to "so-called class 1" drugs. H. R. Rep. No. 98-857 (Part 1), 98th Cong., 2d Sess. 38 (reprinted in 1984 U.S. Code Cong. & Admin. News 2647, 2671. There is no dispute that the statutory references to drugs that contain "no previously approved active ingredient (including any ester or salt of the active ingredient)" are meant to refer to "new molecular entities" or "Type 1" drugs as then defined in the NDA classification scheme set forth in the Bureau of Drugs Staff Manual Guide 4820.3 (1982) (Attachment C).

The 1982 Staff Manual Guide provided two classifications for drug products that contain new active ingredients. The class of drugs referred to as "Type 1" drugs or "new molecular entities" was limited to new active ingredients that contain new therapeutic moieties. The second classification was denominated "Type 2" or "new salt." Staff Manual Guide 4820.3 at 2. This category was not limited to salts, however, but rather included any new salt, ester, or derivative. Id. See also statement of Marion J. Finkel, M.D., Director, Bureau of Drugs, FDA, 302 N.E.J.M. 181 (1980) ("[Drugs] are rated on the newness of the entity – on whether, for example, they are new molecular entities or new salts, esters, or other derivatives of an already marketed product . . . .") (Attachment D). Salts and esters are, of course, themselves derivatives. Thus, the classification scheme was based essentially on a distinction between derivatives and new molecular entities. Derivatives of

previously approved compounds were classified along with new salts, rather than as new molecular entities.

Consistent with Congress' reference to this classification scheme, FDA's regulations limit five-year exclusivity to drugs with new active moieties. In defining the term "active moiety," however, the agency did not adopt the definition of Type I drugs found in the Staff Manual Guide. Rather than excluding "all salts, esters, or derivatives," as in the definition of new molecular entities, the definition in the regulations excludes salts, esters, and "noncovalent derivatives."[3] Under this wording, all covalent derivatives other than esters would be deemed new active moieties entitled to five-year exclusivity.

There is no basis in the statute or in the legislative history for awarding five-year exclusivity based on the distinction between a covalent and noncovalent bond. The statutory exclusivity provisions clearly exclude not only salts, which are noncovalent derivatives, but also esters, which are covalent derivatives. Moreover, as noted above, Congress intended this exclusivity to be available only to Type I drugs as defined by FDA when the legislation was passed. In 1984, the definition of Type I drugs did not distinguish between covalent and noncovalent derivatives.

Congress clearly did not intend to award this extraordinary marketing monopoly on the mere basis of the ability of a company being able to develop a derivative with a covalent rather

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[3] The regulations provide in relevant part:

> *Active moiety* means the molecule or ion, excluding those appended portions of the molecule that cause the drug to be an ester, salt (including a salt with hydrogen or coordination bonds), or other noncovalent derivative (such as a complex, chelate, or clathrate) of the molecule, responsible for the physiological or pharmacological action of the drug substance.

21 C.F.R. 314.108(a).

than noncovalent bond.[4] In the case of derivatives, exclusivity must be based on the significance of the modification on drug activity rather than on the nature of the molecular bond.

It is even less credible to argue that Congress intended to award five-year exclusivity to a derivative merely because it is a metabolite. The statutory exclusivity provisions clearly exclude acids of previously approved esters, many of which are metabolites.[5] Moreover, the exclusion for salts, esters, and noncovalent derivatives derives from the fact that these structural changes are not intended to and generally do not alter the basic pharmacologic or toxicologic properties of the molecule because the same moiety or ion goes to the site of drug action. The same can generally be said for an active metabolite of a previously approved parent compound. If there is to be a *per se* rule relative to an active metabolite of a previously approved compound it should be the same as the rule that is applied to acids and esters because there is no basis for a presumption that the structural differences between the two are significant enough to warrant five year exclusivity.

The potential significance of modifications of covalent structure is reflected in the amount and kind of data required for approval of drugs embodying such modifications. Clearly, however, the mere presence of clinical data does not automatically lead to five year exclusivity. On the contrary the statute provides three year exclusivity, and not five year exclusivity, in instances where

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[4] While the agency explained that noncovalent derivatives "generally [do] not affect the active moiety of a drug product," 59 Fed. Reg. 50335, 50358, there is no basis in science for assuming that covalent derivatives, as a class, have therapeutic moieties that are different from those of their parent compounds.

[5] There is, in the preamble to the proposed regulations, language suggesting that molecular derivatives are entitled to five year exclusivity if they can be characterized as metabolites of previously approved drugs. 54 Fed. Reg. at 28898 (1989) ("A compound (other than an ester) that requires metabolic conversion to produce an already approved active moiety is considered a 'new molecular entity,' however, and will be considered a new chemical entity entitled to 5 years of exclusivity."). However, there is no basis in the statute, its legislative history, or in science for awarding exclusivity based solely on a determination that the new active ingredient is a metabolite of a previously approved active ingredient, or vice versa. The relationship between the terfenadine and its active metabolite TAM is the same as the relationship between an ester and an acid. Both the terfenadine and the ester are vehicles for delivering other active ingredients, TAM and the acid, respectively. This reasoning that precludes exclusivity in the case of the ester/acid relationship likewise precludes exclusivity for TAM. Moreover, as in the case of TAM, the metabolite is the active agent of the parent compound.

significant clinical studies are required in support of an innovative change in a drug. It may be that the TAM NDA contains reports of new clinical investigations essential to the approval of TAM. If so, three year exclusivity may be in order if the statutory criteria are met.[6] It is clear, however, that the modifications embodied in the TAM covalent structure are so slight as to allow extensive reliance by the TAM applicant on its existing terfenadine data. Clearly the approval of TAM does not require the amount and type of safety and effectiveness data required for a new active moiety. Therefore, five year exclusivity is simply not in order.

It should be noted that the Drug Price Competition and Patent Term Restoration Act of 1984 was intended in part to provide periods of exclusivity as a reward for innovator drug companies for the time and expense incurred in undertaking to gain marketing authorization from FDA. In connection with TAM, however, the NDA applicant has already availed itself of an advantage in terms of time and expense by reference to its own NDA for a related compound. It would be at odds with legislative intent for FDA to grant the further advantage of five years exclusivity in a situation where the NDA applicant has not been required to undertake the full range of studies required for a *bona fide* new chemical entity.

The agency's decision to grant five-year exclusivity to all covalent derivatives as a class is also at odds with judicial construction of the exclusivity provisions of the Act. In cases involving exclusivity for new molecular entities, the courts have narrowly interpreted the scope of exclusivity because, in the words of the United States Court of Appeals for the District of Columbia Circuit, "[t]he purpose of [the 1984 Amendments] was to increase competition in the drug industry by facilitating the approval of generic copies of drugs." Mead Johnson Pharmaceutical Group v. Bowen, 838 F.2d 1332, 1333 (D.C. Cir. 1988). See also Norwich Eaton Pharmaceuticals, Inc. v. Bowen, 808 F.2d 486, 488 (6th Cir. 1987). Awarding exclusivity to such a broad class of drugs is further inconsistent with the agency's statement in the preamble to the proposed regulations that "FDA will consider whether a drug contains a previously approved active moiety on a case-by-case basis." 54 Fed. Reg. at 28898.[7]

Thus, the provisions in the regulations that provide five-year exclusivity to all covalent derivatives other than esters are arbitrary and capricious and are without foundation in law. See

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[6] 21 U.S.C. 355(c)(3)(D)(iii); (j)(4)(D)(iii). See also 54 Fed. Reg. at 28899-28901.

[7] The agency made this statement following a discussion of the definition of active moiety in which the agency paraphrased the wording of the current regulation. 54 Fed. Reg. at 28898.

Arent v. Shalala, 70 F.3d 610, 615-16 (D.C. Cir. 1995); Ames Community Hospital, Inc. v. Shalala, 21 F.3d 1176, 1178-80 (D.C. Cir. 1994); National Nutritional Foods Ass'n. v. Matthews, 557 F.2d 325, 330-331 (2d Cir. 1977). In this regard, the agency's regulations fail to meet the requirements of the Administrative Procedure Act, 5 U.S.C. § 551, et seq., and are without force and effect of law. Chevron U.S.A. Inc. v. Natural Resources Defense Fund, Inc., 467 U.S. 837, 842-45 (1984); U.S. v. Nova Scotia Foods Prod. Corp., 568 F.2d 240, 245 (2d Cir. 1977). The agency has no legal authority to grant five-year exclusivity to covalent derivatives (or to a parent compounds of covalent derivatives) that contain previously approved therapeutic moieties.

3. FDA MUST PROVIDE A NOTICE IN THE FEDERAL REGISTER OF THE CHANGE IN POLICY REQUIRED TO MAKE FIVE-YEAR EXCLUSIVITY DETERMINATIONS IN ACCORDANCE WITH LAW

The implementation of the five-year exclusivity provisions of the Act consistent with these legal requirements will necessitate a change in FDA policies stated in regulations and in preambles. Because these policies have been published in Federal Register notices, the change in policy must be announced in a Federal Register notice. The notice should provide, in substance, as follows:

(1) Five-year exclusivity is available only to new active ingredients that contain entirely new therapeutic moieties.

(2) The therapeutic moiety, for purposes of entitlement to five-year exclusivity, is the molecular component that is responsible for the drug effect.

(3) Active ingredients that are metabolites of previously approved active ingredients do not in all instances contain new therapeutic moieties.

(4) A metabolite is entitled to five-year exclusivity only if its therapeutic moiety is not present and not responsible for the drug effect in a previously approved product.

Companies whose interests are affected by FDA's application of the exclusivity provisions of the Act are entitled to notification of changes in policy at the earliest possible time. The agency must also consider whether these changes in policy require the immediate promulgation of an

interim rule redefining the term active moiety to encompass only the concept of therapeutic moiety, as described above.

4. FDA SHOULD DECLARE THAT TAM IS INELIGIBLE FOR FIVE-YEAR EXCLUSIVITY.

Although the agency generally makes exclusivity decisions at or near the date of approval for a product, the agency can make this determination at an earlier date with regard to five-year exclusivity, which is based on criteria (the structure and functional components of the molecule) that are known and are not subject to change during the approval process. The moiety of the TAM molecule that is responsible for its drug action is identical to, and performs the same function as, the therapeutic moiety of the terfenadine molecule.

It is significant that the applicant submitting the TAM NDA has brought suit against generic drug companies that wish to market terfenadine, alleging that administration of terfenadine constitutes infringement of a patent claiming TAM. See Marion Merrell Dow, Inc. v. Geneva Pharmaceuticals, Inc., 33 USPQ2d 1673 (D.C. Col. 1994); Marion Merrell Dow, Inc. v Baker Norton Pharmaceuticals, Civ. No. 94-1245 (S.D. Fla. June 20, 1994). Marion relies upon the theory of contributory infringement on the basis that terfenadine converts after being ingested into TAM, a compound claimed in the patent in suit. The position of the TAM NDA applicant in these cases, equating administration of terfenadine with administration of TAM, is entirely inconsistent with a determination that two compounds possess different active moieties. The relationship between terfenadine and TAM is so close that TAM cannot reasonably be characterized as a new active moiety.

Based on these facts, TAM is not entitled to five-year exclusivity under the Act and, accordingly, FDA cannot award such exclusivity. These facts are not subject to change during the approval process. Just as the agency must move expeditiously to publish a notice of the required change in policy, the agency should inform the holder of the TAM application, as well as other companies with an interest in TAM or terfenadine, of the effect of the policy change on TAM's eligibility for five-year exclusivity.

C. ENVIRONMENTAL IMPACT

According to 21 C.F.R. § 25.24(a)(8), this petition qualifies for a categorical exclusion from the requirement for submission of an environmental assessment.

D. ECONOMIC IMPACT

According to 21 C.F.R. § 10.30(b), information on economic impact will be submitted if requested by the Commissioner following review of this petition.

E. CERTIFICATION

The undersigned certifies, that, to the best knowledge and believe of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner which are unfavorable to the petition.

Respectfully submitted,

Arthur Y. Tsien
Tish E. Pahl
Olsson, Frank & Weeda, P.C.
Suit 400
1400 Sixteenth Street, N.W.
Washington, D.C. 20036-2220

Attachments:

A – Seldane® labeling
B – FDA guidance, "Terfenadine Tablets In Vivo Bioequivalence and In Vitro Dissolution"
C – Bureau of Drugs Staff Manual Guide 4820.3 (1982)
D – 302 N.E.J.M. 181 (1980)

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August 12, 1996

Dockets Management Branch
Food and Drug Administration
Room 1-23
12420 Parklawn Drive
Rockville, MD 20857

'96 AUG 12 P12:32

Re: Docket No. 96P-0157
Citizen Petition
Eligibility of Fexofenadine
For Five-year Exclusivity

Dear Sir or Madam:

Pursuant to 21 C.F.R.§10.30(d), the following comments in opposition to the above referenced citizen petition dated May 17, 1996 are submitted on behalf of Hoechst Marion Roussel Inc. ("HMR").

On July 25, 1996, FDA approved HMR's NDA 20-625 for Allegra (fexofenadine), the first drug product containing fexofenadine which has been approved by the agency. This application was designated as a 1S drug by FDA, meaning that the agency classified it as a new chemical entity entitled to five year exclusivity. HMR believes that this agency's decision was correct, and that this petition seeking to reverse the decision should be denied, for the reasons given below.

I. Fexofenadine Is Entitled To 5 Year Exclusivity Under FDA's Regulations

The most important fact relevant to the issue raised as to fexofenadine exclusivity is that, under the FDA regulations, Section 314.108, the first drug product containing this compound is clearly entitled to 5 year exclusivity. Petitioner appears to recognize this in requesting a new "policy" but fails explicitly to request that the regulation be amended, as it would have to be to accommodate Petitioner's position. In later sections of these comments, we point out that the present regulations are a reasonable interpretation of the statutory requirement and that the "policy" suggested by Petitioner would be unreasonable and burdensome to the agency.

Section 314.108(b)(2) provides for 5 year exclusivity for a drug product containing a "new chemical entity" approved after September 24, 1984. "New chemical entity" is defined in Section 314.108(a) as a drug not containing an "active moiety" which was previously granted new drug approval by FDA. "Active moiety" in turn is defined in Section 314.108(a) as

> the molecule or ion, excluding those appended portions of the molecule that cause the drug to be an ester, salt (including a salt with hydrogen or coordination bonds), or other noncovalent derivatives (such as a complex, chelate, or clathrate) of the molecule, responsible for the physiological or pharmacological action of the drug substance

Fexofenadine (also known as terfenadine acid metabolite or TAM) has not been approved in any new drug application in the United States other than the present approval obtained by Hoechst Marion Roussel. The only question raised by Petitioner as to its entitlement to 5 year exclusivity is based on its relationship to terfenadine, which is contained in a previously approved drug product, Seldane. Fexofenadine is an acid metabolite of terfenadine formed after terfenadine is processed by the liver. It is not a salt or ester of terfenadine or a noncovalent derivative of terfenadine.[1] It thus is not the same active moiety as terfenadine under the above quoted definition and is a new chemical entity entitled to five year exclusivity under Section 314.108(b) and under Section 505(j)(4)(D)(ii) of the Federal Food, Drug and Cosmetic Act.

Petitioner does not dispute any of the above facts but argues that fexofenadine <u>should</u> be considered the same active

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[1] Petitioner makes various unsupported statements and conjectures concerning pharmacological and chemical properties of terfenadine and fexofenadine in an obvious and erroneous attempt to trivialize and oversimplify the differences between these compounds. Since these statements are irrelevant to the determination of the issues under consideration, it is not necessary to discuss them other than to state for the record that we do not agree with them. The chemical and pharmacological properties of terfenadine and fexofenadine are accurately described in the respective NDAs for terfenadine (Seldane) and fexofenadine (Allegra). Needless to say, Petitioner's efforts at comparing the terfenadine molecule with the fexofenadine molecule are specious. Even slight changes in a molecular structure very often lead to significant and unpredictable changes in activity, underscoring the rationality of the agency's regulations in defining a new chemical entity.

moiety as terfenadine so that it will not be entitled to 5 year exclusivity. As noted above, FDA has already decided to the contrary in approving Allegra (fexofenadine) as a 1S drug entitled to 5 year exclusivity on July 25, 1996. For the reasons given below, this decision was consistent with good policy and should not be overturned.

II. FDA's Regulations Are A Reasonable Interpretation Of The Act

Section 505(j)(4)(D)(ii) of the Federal Food, Drug and Cosmetic Act provides that there shall be 5 year exclusivity for a drug if "no active ingredient (including any ester or salt of the active ingredient)" was previously approved in another application.

By this language, Congress clearly intended that a salt or ester of an active ingredient should be treated the same as the ingredient itself. However, nothing was said to suggest that other related compounds, including metabolites which were not salts or esters, were to be so treated. The Congress could have broadened the concept to include all metabolites, or all compounds related in various other ways to the previously approved compound but chose not to do so. This is reasonable in that the relationships of salts and esters to the compound from which they are formed is specific and well defined. Many other related compounds such as metabolites may differ from the compound from which they are formed in many different ways, the effects of which in many cases are much less well established. In any case, Congress drew a line placing salts and esters together with the active ingredient from which they were formed but placing other related compounds, including metabolites which are not salts or esters, outside that line. In drawing this line, the Congress may have been influenced, as Petitioner suggests, by the amount of new safety and effectiveness data required for approval of the related compound. However that may be, a legislative line was drawn and that line must be respected regardless of arguments as to why a different line should have been chosen instead or why it might be unfair in a particular case.[2]

---

[2] There is no reason why treating a metabolite as a different chemical entity than the drug from which it was metabolized is unfair. Indeed, FDA has already done this in a very similar situation with respect to another recently approved antihistamine cetirizine hydrochloride (Zyrtec) which is the acid metabolite of hydroxyzine hydrochloride, a previously approved drug. See Simons, The Pharmacology and Use of H1-Receptor-Antagonist Drugs, New Eng.J.Medicine, Vol. 330, No.23, p. 1663, 1665 (1994); Goodman & Gilman, *The Pharmacological Basis of*

FDA's regulations are clearly based on the statutory language and are a reasonable interpretation of that language. They accept and implement the statutory inclusion of salts and esters with the compound from which they were formed and do not include other related compounds such as metabolites (which are not salts or esters) which the statute did not include. The only difference from the statute is the inclusion of chelates, clathrates, and other noncovalent derivatives which are very similar to salts and esters in that they generally do not affect the active moiety of the drug product. Whether or not these additional inclusions are consistent with the statutory provision, they are not relevant to the fexofenadine/terfenadine issue.

Petitioner's suggestion that the definition of "active moiety" include covalent derivatives as well as noncovalent derivatives is not consistent with the statutory language providing only for the inclusion of salts and esters and not other related compounds. Moreover, as explained below, even assuming that the FDA inclusion of noncovalent derivatives was proper, covalent derivatives are a much larger class of related compounds, vaguely defined and clearly beyond the intent of Congress to include.

Thus, FDA's regulations are a reasonable interpretation of the statutory language and Petitioner's suggested amendment to the regulation would not be consistent with the statute.

Therapeutics (9th ed.), p. 591. Cetirizine hydrochloride has been granted 5 year exclusivity. See *Approved Drug Products With Therapeutic Equivalence Evaluations* (16th ed.), p. AD16. There also are many other instances in which FDA has treated metabolites as different drugs than the substance from which they were metabolized, such as prednisone and prednisolone.

Also, in this case the safety profile of fexofenadine is significantly different from terfenadine. The drugs have markedly different effects in the human body, particularly with regard to QT prolongation. Thus, FDA has required extensive new safety and effectiveness studies for fexofenadine. This exposes as without merit Petitioner's attempt to trivialize the differences in chemical structure between terfenadine and fexofenadine. These differences and the physiological differences found between the two compounds further support the rationality of the agency's regulations both in general and on the particular facts raised here.

III. Petitioner's Suggested "Policy" Would Lead To Uncertainty And Be Burdensome To The Agency

Petitioner claims that granting 5 year exclusivity for fexofenadine is unfair but does not state or even suggest any reasonable rule under which this result would be avoided.

Petitioner suggests that FDA should accept and implement Petitioner's positions that:

> Metabolites of previously approved drugs are not entitled to 5 year exclusivity unless they are demonstrated to contain new therapeutic moieties.
>
> Active ingredients that are metabolites of previously approved active ingredients do not in all instances contain new therapeutic moieties.
>
> A metabolite is entitled to five-year exclusivity only if its therapeutic moiety is not present and not responsible for the drug effect in a previously approved product.

However, Petitioner does not offer any rule for determining what is a new therapeutic moiety or what therapeutic moiety is present or responsible for the drug effect in a previously approved product.

Aside from the lack of any statutory basis for it, what Petitioner suggests is completely unworkable because there would be no reliable way to determine which metabolites are new therapeutic moieties. Like covalent derivatives generally, the scope of the concept of "metabolites" is extremely broad in a chemical sense, i.e., there is no way of telling, simply by looking at chemical structures, whether compounds are or may be metabolites of each other. Thus, for each application there would have to be a specific determination by FDA as to whether there was a new therapeutic moiety and there would in almost every case be either an applicant or another interested party standing by to contest FDA's determination. Further, these determinations would have to be constantly reviewed and possibly revised by the agency in light of new scientific knowledge concerning metabolites of drug products. The uncertainty and administrative burden on FDA and the contesting parties of such a system is obvious and clearly undesirable.

FDA's current regulations provide for a perfectly straight forward determination based on application of simple chemical concepts, of whether one drug contains the same active moiety as another. There is no reason to change this situation simply to accommodate Petitioner's desire that fexofenadine be denied 5

year exclusivity.

Conclusion

For the foregoing reasons, the above-referenced petition should be denied.

Respectfully submitted,

Peter O. Safir
Richard S. Morey

Counsel for Hoechst Marion Roussel Inc.

POS/RSM/r

FORM PTO-1595
1-31-92
(modified)

RECORDATION FORM COVER SHEET
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PATENT AND TRADEMARK OFFICE

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Date 15 August 1996

Signature Janet Grubb

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1. Name of conveying party(ies): Richardson-Merrell Inc.
Additional name(s) of conveying party(ies) attached? [ ] Yes [X] No

2. Name and address of receiving party(ies):
Name: Merrell Dow Pharmaceuticals Inc.
Internal Address:
Street Address: 2110 E. Galbraith Road
City: Cincinnati State: Ohio ZIP: 45215
Additional name(s) & address(es) attached? [ ] Yes [X] No

3. Nature of Conveyance:
[ ] Assignment [ ] Merger
[ ] Security Agreement [X] Change of Name
[ ] Other _____

Execution Date: March 10, 1981

4. Application number(s) or patent number(s):
If this document is being filed together with a new application, the execution date of the application is:

A. Patent Application No.(s):

B. Patent No.(s): 4,254,129

Additional numbers attached? [ ] Yes [X] No

5. Name and address of party to whom correspondence concerning document should be mailed:
Name: Louis J. Wille
Internal Address: Hoechst Marion Roussel, Inc.
Street Address: 2110 E. Galbraith Rd.
City: Cincinnati State: Ohio ZIP: 45215

Our Reference No.: M00956

6. Total number of applications and patents involved: [1]

7. Total fee (37 CFR 3.41): 40.00
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To the best of my knowledge and belief, the foregoing information is true and correct and any attached copy is a true copy of the original document.

Louis J. Wille — Name of Person Signing

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8/14/96 — Date

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State of DELAWARE

Office of SECRETARY OF STATE

I, Glenn C. Kenton *Secretary of State of the State of Delaware, do hereby certify that the above and foregoing is a true and correct copy of* Certificate of Merger of the "DOW MERGER SUB INCORPORATED", merging with and into the "Richardson-Merrell Inc.", under the name of "Merrell Dow Pharmaceuticals Inc.", as received and filed in this office the tenth day of March, A.D. 1981, at 11:15 o'clock A.M.

In Testimony Whereof, *I have hereunto set my hand and official seal at Dover this* tenth *day of* March *in the year of our Lord one thousand nine hundred and* eighty-one.

Glenn C. Kenton

Glenn C. Kenton, Secretary of State

FORM 121

CERTIFICATE OF MERGER
of
DOW MERGER SUB INCORPORATED
into
RICHARDSON-MERRELL INC.

UNDER SECTION 251 OF THE GENERAL CORPORATION LAW OF THE STATE OF DELAWARE

Pursuant to Section 251(c) of the General Corporation Law of the State of Delaware, Richardson-Merrell Inc., a Delaware corporation ("RMI"), hereby certifies the following information relating to the merger of Dow Merger Sub Incorporated, a Delaware corporation ("Dowsub"), with and into RMI (the "Merger").

1. The names and states of incorporation of RMI and Dowsub, which are the constituent corporations in the Merger (the "Constituent Corporations"), are:

Name	State
Richardson-Merrell Inc.	Delaware
Dow Merger Sub Incorporated	Delaware

2. The Agreement and Plan of Reorganization, dated as of November 1, 1980, as amended February 4, 1981, by and among RMI, Dowsub and The Dow Chemical Company, a Delaware corporation (the "Merger Agreement"), setting forth the terms and conditions of the Merger, has been approved, adopted, certified, executed and acknowledged by each of the Constituent Corporations in accordance with the provisions of Section 251(c) of the General Corporation Law of the State of Delaware.

3. The name of the corporation surviving the Merger is Richardson-Merrell Inc. which shall, at the Effective Time, be named "Merrell Dow Pharmaceuticals Inc."

4. Pursuant to the Merger Agreement, the Certificate of Incorporation of RMI in effect immediately prior to the Effective Time of the Merger (as defined in the Merger Agreement) shall be the Certificate of Incorporation of the surviving corporation; provided, however, that:

(a) Article FIRST of such Certificate shall be amended at the Effective Time to read in its entirety *in haec verba:* "The name of the corporation is Merrell Dow Pharmaceuticals Inc. (hereinafter sometimes called the 'Corporation')"; and

(b) Article FOURTH of such Certificate shall be amended at the Effective Time to read in its entirety *in haec verba*: "The total number of shares of all classes of stock which the Corporation shall have authority to issue is 1,000, and all 1,000 shares shall consist of Common Stock, par value $.10 per share."

5. An executed Merger Agreement is on file at the principal place of business of the surviving corporation, which is located at 2110 East Galbraith Road, Cincinnati, Ohio 45215.

6. A copy of the Merger Agreement will be furnished by the surviving corporation, on request and without cost, to any stockholder of either of the Constituent Corporations.

IN WITNESS WHEREOF, this Certificate of Merger has been executed on this 10th day of March, 1981.

RICHARDSON-MERRELL INC.

By H S Richardson Jr.
Chairman of the Board

[CORPORATE SEAL]

Attest:

Secretary

COPY

FORM PTO-1595
1-31-92
(modified)

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Date 15 August 1996

Signature Janet Grubb

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1. Name of conveying party(ies): Merrell Dow Pharmaceuticals Inc.

Additional name(s) of conveying party(ies) attached? [ ] Yes [X] No

2. Name and address of receiving party(ies):

Name: Merrell Pharmaceuticals Inc.
Internal Address:
Street Address: 2110 E. Galbraith Road
City: Cincinnati State: Ohio ZIP: 45215

Additional name(s) & address(es) attached? [ ] Yes [X] No

3. Nature of Conveyance:

[ ] Assignment [ ] Merger
[ ] Security Agreement [X] Change of Name
[ ] Other _____

Execution Date: September 15, 1995

4. Application number(s) or patent number(s):
If this document is being filed together with a new application, the execution date of the application is:

A. Patent Application No.(s):

B. Patent No.(s): 4,254,129

Additional numbers attached? [ ] Yes [X] No

5. Name and address of party to whom correspondence concerning document should be mailed:

Name: Louis J. Wille
Internal Address: Hoechst Marion Roussel, Inc.
Street Address: 2110 E. Galbraith Rd.
City: Cincinnati State: Ohio ZIP: 45215

Our Reference No.: M00956

6. Total number of applications and patents involved: [1]

7. Total fee (37 CFR 3.41): 40.00

[ ] Enclosed
[X] Authorized to be charged to deposit account

8. Deposit account number: 13-2764

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9. Statement and signature.

To the best of my knowledge and belief, the foregoing information is true and correct and any attached copy is a true copy of the original document.

Louis J. Wille — Louis J. Wille — 8/14/96

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State of Delaware

Office of the Secretary of State

I, EDWARD J. FREEL, SECRETARY OF STATE OF THE STATE OF DELAWARE, DO HEREBY CERTIFY THE ATTACHED IS A TRUE AND CORRECT COPY OF THE CERTIFICATE OF AMENDMENT OF "MERRELL DOW PHARMACEUTICALS INC.", CHANGING ITS NAME FROM "MERRELL DOW PHARMACEUTICALS INC." TO "MERRELL PHARMACEUTICALS INC.", FILED IN THIS OFFICE ON THE TWENTY-SECOND DAY OF SEPTEMBER, A.D. 1995, AT 10 O'CLOCK A.M.

Edward J. Freel, Secretary of State

0326521 8100

AUTHENTICATION: 7660652

950225229

DATE: 10-02-95

9-12-95

CERTIFICATE OF AMENDMENT TO CERTIFICATE OF INCORPORATION OF MERRELL DOW PHARMACEUTICALS INC.

The undersigned, Richard J. Markham, President and Chief Executive Officer, and Rebecca R. Tilden, Secretary of Merrell Dow Pharmaceuticals Inc., a corporation organized and existing under the laws of the State of Delaware (hereinafter sometimes referred to as the "Corporation"), do hereby certify as follows:

FIRST: That the Board of Directors of the Corporation duly proposed the following amendment to the Certificate of Incorporation of the Corporation, duly adopted a resolution setting forth the proposed amendment, subject to approval of the shareholder of the Corporation:

RESOLVED, that the Certificate of Incorporation of Merrell Dow Pharmaceuticals Inc., a Delaware corporation, (the "Certificate of Incorporation"), shall be, and it hereby is, amended by deleting all of paragraph 1 thereof and by inserting, in lieu thereof, a new paragraph 1 providing in its entirety as follows:

FIRST: The name of the corporation is MERRELL PHARMACEUTICALS INC. (hereinafter sometimes called the "Corporation").

SECOND: That by Statement of Unanimous Consent the shareholder of the Corporation voted in favor of the amendment and that said amendment was duly adopted.

THIRD: That the capital of the Corporation will not be reduced under or by reason of said amendment.

FOURTH: That, accordingly, the amendments to the Certificate of Incorporation of Merrell Dow Pharmaceuticals Inc., as hereinbefore set forth in Article FIRST of this Certificate of Amendment, has been duly adopted in accordance with the provisions of Section 242 of the General Corporation Law of the State of Delaware.

IN WITNESS WHEREOF, we, Richard J. Markham, President and Chief Executive Officer, and Rebecca R. Tilden, Secretary of Merrell Dow Pharmaceuticals Inc., Inc., have signed this Certificate under the corporate seal of the Corporation (thereby acknowledging, under penalties of perjury, that the

foregoing instrument is their act and deed and that the facts stated therein are true) on the 15th day of September, 1995.

Merrell Dow Pharmaceuticals Inc.

Richard J. Markham
President and Chief Executive Officer

(CORPORATE SEAL)

ATTEST:

Rebecca R. Tilden, Secretary

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